REMARKS

In the Office Action mailed December 17, 2003, the Examiner rejected claims 1, 4-6, and 9-11 under 35 U.S.C. § 103(a) as being unpatentable over Nasir et al., *Combinatorial Chemistry & High Throughput Screening* ("Nasir") in view of Pestka et al., *Food Technology* ("Pestka"), rejected claims 2 and 7 under 35 U.S.C. § 103(a) as being unpatentable over Nasir, in view of Pestka, and further in view of Michel et al., U.S. Patent No. 5,741,654 ("Michel"), rejected claims 3 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Nasir, in view of Dixon, and in further view of McMahon et al., U.S. Patent No. 5,166,078 ("McMahon"), and rejected claims 10-11 under 35 U.S.C. § 103(a) as being unpatentable over Nasir in view of Pestka and Zuk et al., U.S. Patent No. 4,281,061 ("Zuk").

The Examiner rejected claims 1 and 5 under 35 U.S.C. § 112, ¶ 1 based on an alleged lack of enablement.

The Examiner rejected 1-4 and 5-9 under 35 U.S.C. § 112, ¶ 2 as being indefinite because of allegedly unclear language in claims 1 and 5.

For the reasons set forth below, Applicants traverse the claim rejections and request reconsideration.

I. Rejections Under 35 U.S.C. § 112, ¶ 1

The Examiner rejected claims 1 and 5 under 35 U.S.C. § 112, ¶ 1 on the basis that the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. However, the Examiner's rejection appears to be based on a number of misconceptions.

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First, the Examiner states that "[t]he specification, supported by applicant's arguments and declaration only provide support for the 6-aminofluorescein fluorophore." That statement is wrong. Although the application discloses results using the particular fluorophore 6-aminofluorescein, the application also incorporates by reference U.S. Patent Nos. 5,427,960 and 5,976,820, which identify a wide range of other fluorophores. Moreover, the application states: "Other fluorophores could also be used, depending on the antibody." (see page 8, line 4).

Second, the Examiner states that "[a]pplicant has also provided arguments and a declaration stating that only the 6-aminofluorescein fluorophore is able to be bind selected antibodies used in the Fluoresecence Polarization Assay – asserting that only a certain fluorophore, conjugated to DON would produce a detectable change in fluorescence polarization." That statement is wrong. The Response and Declaration filed with the RCE do not state that only 6-aminofluorescein would produce a detectable change in fluorescence polarization. To the contrary, the Response and Declaration noted that later research found that 4'-(aminomethyl) fluorescein could also be used in a fluorescence polarization assay for DON.

Finally, the Examiner asked where specification support could be found for the use of other fluorophores. As noted above, the specification incorporates by reference two U.S. patents that identify a wide range of fluorophores. Moreover, the specification indicates that "[o]ther fluorophores could also be used, depending on the antibody." (see page 8, line 4).

Because the Examiner's rejections under 35 U.S.C. § 112, ¶ 1 are premised on a number of misconceptions, Applicants respectfully submit that the rejections are improper and should be withdrawn. The claims clearly meet the requirements of 35 U.S.C. § 112, ¶ 1.

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II. Rejections Under 35 U.S.C. § 112, ¶ 2

The Examiner rejected claims 1-4 and 5-9 under 35 U.S.C. § 112, ¶ 2 as being indefinite. In particular, the Examiner stated that some of the language in claims 1 and 5 was confusing. In response, Applicants have amended claims 1 and 5 to make clear that the tracer comprises a fluorophore conjugated to DON. Accordingly, Applicants submit that with these amendments, claims 1 and 5 meet the requirements of U.S.C. § 112, ¶ 2.

III. Claim Rejections Under 35 U.S.C. § 103(a)

A. The Examiner Has Not Made A *Prima Facie* Case of Obviousness

With respect to the Examiner's rejections of the claims under § 103, Applicants submit that the Examiner has not established a *prima facie* case of obviousness, for the reasons set forth in Applicants' previously-filed "Response to Office Action Mailed October 17, 2002" and "Response to Office Action Mailed July 7, 2003." Rather than repeat those arguments in their entirety, Applicants make the following additional points.

First, as the motivation for combining the Pestka and Nasir references, the Examiner relies on Pestka's teaching that "DON and its derivative trichothecenes ... are a health hazard to humans and animals and therefore needs to be tested to determine safe and toxic levels in food." The flaw in the Examiner's argument is that Pestka teaches that immunoassay kits for testing for deoxynivalenol and T-2 toxin (another trichothecene) in various food products were already commercially available. (see Table 4 on p. 126 of Pestka). Indeed, one of the deoxynivalenol immunoassay kits listed in the table is described as "USDA-FGIS certified." Thus, Pestka teaches that the need for testing for DON and derivative trichothecenes in food products was already met. Accordingly, Examiner's rationale is insufficient to explain why one of ordinary

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skill in the art would be motivated to develop fluorescence polarization based assays for DON and derivative trichothecenes.

Second, one of the requirements for a *prima facie* case of obviousness is a reasonable expectation of success, which must be found in the prior art and not based on the applicants' disclosure. *See* MPEP § 706.02(j). The Examiner has not satisfied this requirement. In particular, Pestka notes that mycotoxins "have a wide array of chemical structures." (see paragraph 1 on p. 120). Moreover, Pestka makes clear that there are many different types of mycotoxins other than trichothecenes, e.g., aflatoxins, cyclopiazonic acid, fumonisins, ochratoxin, patulin, zearalenone, ergot alkaloid, fusarochromanone, PR toxin, rubratoxin, and sterigmatocystin. Given the significant number of different types of mycotoxins, and the wide array of chemical structures that mycotoxins have, the statements in Nasir regarding mycotoxins cannot be interpreted as teaching a reasonable expectation that fluorescence polarization (FP) assays would succeed for each and every type of mycotoxin. Indeed, while the section in Nasir that refers to mycotoxins cites a number of articles, none of the cited articles actually relate to FP assays for mycotoxins, and Nasir does not report any actual results for FP assays for mycotoxins. Thus, the skilled artisan would have recognized from Nasir only that fluorescence polarization was "a technique of great potential in this area of research," not that FP assays could be used successfully for any particular mycotoxin.

B. Evidence of Non-Obviousness

Even assuming that the Examiner has somehow made a proper *prima facie* case of obviousness, Applicants presented substantial evidence of non-obviousness with the Response and Declaration filed with the RCE. However, the Examiner does not appear to have fully considered Applicants' evidence of non-obviousness.

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For example, Applicants submitted the Declaration of Dr. Michael E. Jolley, which pointed out some of the difficulties in developing successful FP assays. The Examiner did not comment on those difficulties, as set forth below:

- Dr. Jolley noted that the "propeller effect" can prevent any change in fluorescence polarization from being observed. Jolley Decl., ¶ 8. The Examiner has not explained how the prior art would have taught one of ordinary skill in the art how to avoid this problem with DON or other trichothecenes.
- Dr. Jolley noted that labeling the antigen to form the fluorescent tracer can also interfere with its ability to bind with the corresponding antibody. Jolley Decl., ¶ 9. The Examiner has not explained how the prior art would have taught one of ordinary in the art how to avoid this problem with DON or other trichothecenes.

Indeed, the inventors themselves encountered such difficulties when trying to develop a fluorescence polarization assay for DON. Three monoclonal antibodies that had been developed for ELISA were tried in a fluorescence polarization for DON. However, in these experiments, which used fluoresceinamine isomer II as the fluorophore, only two of these antibodies worked. Unexpectedly, the antibody that was most sensitive in the ELISA format did not work in the fluorescence polarization format, apparently, because it did not bind to the tracer or because it bound to the tracer without producing a detectable change in fluorescence polarization:

> Three murine monoclonal antibodies developed previously for ELISA applications were tested ... Two of these, produced by reference clones 1 and 4, were capable of interacting with the tracer and increasing the polarization signal while the third antibody (#22) did not. Apparently, antibody 22, which was the most sensitive antibody in the competitive direct ELISA format, either did not bind the tracer or did not affect the polarization of the tracer. Although the remaining two clones were less sensitive in the ELISA format, they nevertheless were very sensitive in the FP immunoassay format.

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C.M. Maragos, M.E. Jolley, and M.S. Nasir, "Flourescence polarization as a tool for the determination of deoxynivalenol in wheat," *Food Additives and Contaminants*, vol. 19, p. 403 (2002); Jolley Decl., ¶ 11.

Under the Examiner's obviousness rationale, antibody #22, which was the most sensitive in the ELISA format, would have been expected to work in the fluorescence polarization format. The fact that antibody #22 did not work when using fluoresceinamine isomer II is powerful evidence of the non-obviousness of selecting a suitable tracer and antibody:

> Absence of property which a claimed invention would have been expected to possess based on the teaching of the prior art is evidence of unobviousness.

See MPEP § 716.02(a). However, the Examiner has not commented on this evidence of non-obviousness. Of course, patentability determinations must be made based on all of the evidence:

> The decision on patentability must be made based upon consideration of all the evidence, including evidence submitted by the examiner and evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence.

See MPEP § 2142. Accordingly, Applicants respectfully request the Examiner to consider all of the evidence that Applicants have submitted.

Once all of the evidence is properly considered, Applicants submit that the patentability of claims 1-11, as amended, is clearly apparent.

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CONCLUSION

Applicants submit that the present application is now in condition for allowance and notice to that effect is hereby requested. Should the Examiner feel that further dialog would advance the subject application to issuance, the Examiner is invited to telephone the undersigned at any time at (312) 913-0001.

Respectfully submitted,

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